



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

(mu)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,000	07/02/2001	Bret A. Ferree	BAF-11302/29	1159
7590	02/25/2004		EXAMINER	
Gifford, Krass, Groh 280 N. Old Woodward Ave., Suite 400 Birmingham, MI 48009			WEGERT, SANDRA L	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/897,000	FERREE, BRET A.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 22 September 2003.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-7 is/are pending in the application.

4a) Of the above claim(s) 5 and 6 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-4 and 7 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 20 October 2003.

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

5) Notice of Informal Patent Application (PTO-152)

6) Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment, filed 24 September 2003, has been entered. Claims 1, 2 and 4 have been amended. The Information Disclosure Statement, submitted 20 October 2003 has been entered into the record. Claims 5 and 6 were previously withdrawn by the examiner (23 April 2003).

Claims 1-4 and 7 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

The objection to Claim 4 for reciting non-elected inventions, as put forth in the previous Office Action (23 April 2003) is *withdrawn*. Applicant amended Claim 4 to remove references to non-elected inventions (20 October 2003).

35 USC § 112, second paragraph – Indefinite terminology.

The rejection of Claims 1 and 7 for reciting the phrase "spinal canal," as set forth in the previous Office Action (page 7, 23 April 2003), is *withdrawn*. Applicant amended Claims 1 and 7 to clarify that growth factors are injected into the central canal of the spinal cord (20 October 2003).

The rejection of Claim 2 because it failed to recite positive method steps involved in "concentrating and releasing the growth or differentiation factors from a patient's blood" or in "obtaining the growth or differentiation factors from recombinant genetic techniques or animal sources" (page 7, 23 April 2003), is *withdrawn*. Applicant amended Claim 2 to recite method steps involved in obtaining growth factors from a patient's blood (20 October 2003).

Maintained Objections and/or Rejections

35 USC § 112, second paragraph – Indefinite terminology.

The rejection of Claim 3 because it failed to recite positive method steps involved in "obtaining the growth or differentiation factors from recombinant genetic techniques or animal sources" (page 7, 23 April 2003), is *maintained*. Applicant discussed use of recombinant growth factors in the response (20 October 2003), but did not discuss how growth factors can be obtained by the recited methods, and did not amend Claim 3.

35 U.S.C. § 112, first paragraph, Enablement.

Claims 1-4 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The reasons for this rejection were set forth at pages 3-5 of the previous office action (23 April 2003). Briefly, the specification is not enabling for the limitations of the claims wherein a

Art Unit: 1647

growth factor or differentiation factor is injected into the spinal cord or disc to treat disc herniation or degenerative disc disease.

Claims 1-4 and 7 read on a method of treating disc herniation or degenerative disc disease, in a patient, by injecting growth factors, such as *BMP-1*, directly into the intervertebral disc or into the spinal cord central canal. Dependent claims recite use of growth factors extracted from a patient's blood or made recombinantly.

However, there is no enabling discussion or working examples disclosed in the instant application that involve injecting growth factors into the spinal cord or into a degenerated or herniated intervertebral disc. The specification discusses spinal anatomy (p. 1-2), disc anatomy (p. 4), and the treatments available (mostly surgical) to correct herniated or degenerating spinal discs (p. 4-5). It also proposes possible treatments of disc degeneration in which a calcium chloride/thrombin mixture is injected into the intervertebral disc or alternatively, a platelet rich plasma/calcium chloride/thrombin mixture is injected. The possible mechanisms underlying such a therapy are not discussed, aside from the statement on page 5: "*the platelets release the soluble regulators/growth factors by adding a mixture of calcium chloride and topical bovine thrombin.*"

However, the claims read on a method of treating disc herniation or degenerative disc disease by injecting a growth factor, such as BMP-1, directly into a vertebral disc or into the spinal cord. There is no enabling discussion or working examples disclosed in the instant application as to how to practice the claimed method of treating disc herniation or degenerative disc disease by injecting BMP-1 into the disc. This lack of enabling data in the instant Specification is particularly important since BMP-1 is a poorly-characterized growth factor

Art Unit: 1647

related to peptides that control or contribute to a *wide variety* of cell growth and differentiation processes (Padgett, et al, 1993, PNAS, 90: 2905-2909). Presumably, the claimed invention seeks to cause growth of connective tissue within the paravertebral disc itself. Yet it is not known if BMP-1 can cause chondrocyte proliferation or production of matrix at all or by itself. Neither is it known if the extent and location of cell proliferation can be controlled by adding BMP-1 into or near the disc. It seems clear that BMP2/4 receptors have been localized to the discs of mice (Takae, et al, 1999, Spine, 24(14): 1397-1401), but how these receptors are related to BMP1 is not known. Furthermore, it is not known the involvement of chondrocytes, fibrocytes, or osteocytes in degenerative disk disease. In addition, BMP-1 is related to a family of growth factors that cause many effects, including cell differentiation and proliferation. It is not known, nor is it predictable, what the precise cellular function of BMP-1 is. In contrast, *BMP-4* has been studied fairly extensively and seems to be involved in body segmentation during development, not in chondrocyte proliferation or differentiation (Padgett, et al 1993, PNAS, 90: 2905-2909). These references and others demonstrate that there is no reason one can infer a specific cellular function for BMP-1, such that the growth factor can be used to treat intervertebral disc herniation or degeneration.

Applicants argue generally that the application does teach the function of BMP's as they relate to a treatment for degenerative disc disease (20 October 2003) presuming then that one of ordinary skill in the art would know how to inject BMP1 into the spinal cord or intervertebral disc in order to treat degenerative disc disease. Applicants refer in particular to an article that discusses the effect of BMP2 on isolated chondrocytes (Yoon, et al, 2003, Spine, 28(16): 1773-1780). In that paper, BMP2, a growth factor that may or may not be closely-related to BMP1,

Art Unit: 1647

was added to isolated rat chondrocytes to cause an increase in expression of several genes known to be related to production or maintenance of extracellular matrix.

Applicant's arguments have been considered, but are not deemed to be persuasive. It is not known how BMP1 might be related to degenerative disc disease. Nor is it predictable the effects of injecting BMP1 into a patient's intervertebral disc as a treatment for degenerative disc disease. Applicants refer to the study of isolated chondrocytes seen in the paper by Yoon, et al (2003, Spine, 28(16): 1773-1780). That paper provided good information as far as the effects of BMP2 on some matrix-forming genes in chondrocytes, but gave little in the way of suggesting a treatment of degenerative disc disease using BMP1 injected into a disc. This is because the function of BMP2 cannot suggest a function for BMP1 (as discussed on page 4 of the previous Office Action; also see Rueger, D., 2002, In: Bone Morphogenetic Proteins, Vukicevic and Sampath, eds., pages 1-18). In addition, experiments with a single type of isolated cell are not enabling for clinical treatment of a disease involving a complex structure containing many types of cells that are interacting in complex ways. Furthermore, such a comparison between the uses of BMP1 and BMP2 in the literature is based entirely on homology. As discussed in the previous office action (pages 4 and 5), one cannot assume a function for a growth factor based on structural similarity to other growth factors. This applies in particular to the family of bone-morphogenetic proteins since they are known to cause varied physiological effects (Rueger, D., 2002, Bone Morphogenetic Proteins, Vukicevic and Sampath, eds., pages 1-18). The instant Specification is lacking in specific information about the effects of BMP's in general, and BMP1 in particular. In addition, it should be kept in mind that post-filing date evidence of enablement

may not refer to materials and methods that were not known in the prior art or disclosed in the Specification at filing.

Applicants conclude their arguments by suggesting: "*The other research regarding the similarities and effects of BMP-n prove that Applicant is entitled to coverage at least with respect to this broad class of biological materials*" (page 6, 22 September 2003). However *Brenner v Manson* (1966, 383 U.S. 519) concluded: "*Unless and until a process is refined and developed to this point--where specific benefit exists in currently available form--there is insufficient justification for permitting an applicant to engross what may prove to be a broad field,*" and "*[a] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion*" (Justice Fortas, writing for the majority).

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation required to determine how to use BMP1 polypeptide to treat degenerative disc disease, the lack of direction or guidance in the specification regarding the same, the lack of working examples that treat a particular condition, the state of the art which is silent concerning the mechanisms of degenerative disc disease, and the breadth of the claims which embrace several methods of treating disc disease --undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Furthermore, as indicated above and in the previous Office Action (23 April 2003) the Specification is not enabling for use of other growth factors for treatment of degenerative disc disease, for the reasons given above for BMP-1 specifically: the BMP family of growth factors has wide-ranging effects; therefore it is not predictable what the effects are for a new or unidentified growth factor.

Applicant is likewise not enabled for a method of treating a degenerative disc disease by making injections into the central canal of the spinal cord. Applicant amended Claim 1 to clarify that the spinal cord injections are into the central canal (20 October 2003) a small cavity in the center of the spinal cord that is filled with cerebral spinal fluid and is contiguous with the cerebral aqueduct system (Kandel, E., Schwartz, J. & Jessell, T. eds, 1991, Principles of Neural Science). However, the cavity is so small compared to the diameter of the spinal cord that it is unlikely that successful injections can be made there (see Kandel, et al page 284). Spinal injections are generally made into the large cistern in the lumbar region below termination of the spinal cord (see Kandel, et al page 285 and 302).

References relied upon for an understanding of the art, but not used in rejections/objections:

- 1) Reddi, H., 2001, Arthritis Res., 3: 1-5.
- 2) Rodan, G. and Martin, T., 2000, Science, 289: 1508-1514.
- 3) Pappano, W., et al, 2003, Mol. Cell. Biol. 23(13): 4428-4438.

Conclusion

No claims are allowed.

Art Unit: 1647

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (571) 272-0887.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

Art Unit: 1647

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW

February 19, 2004

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER